(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 February 2003 (20.02.2003)

PCT

(10) International Publication Number
WO 03/013481 A1

(51) International Patent Classification[7]: A61K 9/66, 47/34

(21) International Application Number: PCT/IB02/03015

(22) International Filing Date: 3 August 2002 (03.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
750/mum/2001 3 August 2001 (03.08.2001) IN

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/013481 A1

(54) Title: THE PROCESS OF MANUFACTURING PHARMACEUTICAL COMPOSITION WITH INCREASED CONTENT OF POORLY SOLUBLE PHARMACEUTICAL INGREDIENTS

(57) Abstract: The present invention relates to a process for solubilizing poorly soluble active pharmaceutical ingredients in a mixture of low molecular and high molecular polyethylene glycol and polyvinyl pyrolidine. The resulting compositions can be encapsulated in a gelatin shell and their capsules provide an effective means for oral delivery of a wide variety of poorly soluble pharmaceutical actives.

THE PROCESS OF MANUFACTURING PHARMACEUTICAL COMPOSITION WITH INCREASED CONTENT OF POORLY SOLUBLE PHARMACEUTICAL INGREDIENTS

Technical Field

The present invention relates to process for manufacturing pharmaceutical composition with increased content of poorly soluble active pharmaceutical ingredients. Poorly soluble active pharmaceutical ingredients needs larger amount of inactives to prepare a clear liquid preparation for encapsulation into a soft gelatin capsule. This necessitates increase in size of a capsule and/or increase in number of capsules to be consumed for a therapeutic effect. The present invention relates to improving the content of poorly soluble active pharmaceutical ingredients in a clear liquid solution.

According to present invention use of two or polyethelene glycol of different molecular weight along with a dispersing agent like vinyl pyrolidone. The resulting solution are clear and remains clear even after encapsulation in a soft gelatin capsule for its self life and beyond.

BACKGROUND OF THE INVENTION

Liquid, and especially concentrated liquid pharmaceutical compositions offer many advantages over solid compositions. Liquids are easy to swallow and provide an excellent vehicle for the uniform delivery of pharmaceutical actives. Liquids provide a rapid onset of pharmacologic action, since the composition does not first have to disintegrate and dissolve in the gastrointestinal tract. Concentrated liquid compositions are ideally suited for encapsulation within a soft gelatin shell, to provide a portable and easy-to-swallow soft, flexible capsule. Encapsulation would also permit the accurate and uniform delivery of a unit dose of a pharmaceutical active, an advantage which becomes especially important when relatively small amounts of an active are to be delivered. Additionally, soft gelatin capsules are aesthetically appealed (especially when filled with a transparent liquid) and can be manufactured in a wide variety of sizes, shapes, and colors.

However, despite these advantages of liquid compositions, it is not always possible to prepare a liquid composition of the desired pharmaceutical active. Many pharmaceutical actives are poorly soluble and therefore require relatively large volumes of solvent for dissolution. Also, the choice of solvents available for use in liquid compositions is limited by safety, compatibility, stability, and economic concerns. Furthermore, the use of large volumes of solvents for solubilizing pharmaceutical actives is undesirable because the resulting solutions would be so dilute as to require impractically large dosages for delivering a therapeutically

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effective amount of active. It would thus be difficult, if not impossible, to encapsulate such large volumes into only one or two gelatin capsules and yet have them be of a reasonable size for easy swallowing.

One approach to overcoming these solubility problems has been to incorporate water, water-miscible co-solvents, and surfactants into the compositions. See, U.S. Pat. No. 4,794,117, to Corbiere, issued Dec. 27, 1988 which discloses the solubiliazation of hydrophobic pharmaceuticals in aqueous solutions of polyethylene glycol at controlled pH; U.S. Pat. No. 4,690,823, to Lohner at al, issued Sep. 1, 1987 which discloses the solubilization of ibuprofen in a mixture of polyethylene glycol and a surfactant; U.S. Pat. No. 3,784,684, to Bossert et al., issued Jan. 8, 1974 which discloses the solubilization of a pharmaceutical active in a mixture of polyethylene glycol and an alcohol having 2-8 carbons and 1-3 hydroxy groups; It is desirable to have poorly soluble drugs like acetaminophen solubilised into a clear solution in as high concentration as possible. It typically involves use of organic solvents.

US patent 5484606 describes the process for reducing the precipitation of difficult to solublize pharmaceutical actives. It used propylene glycol to achieve this purpose along with polyethylene glycol and polyvinyl pyrolidine to achieve this. US patent 5505961 deals with gelatin capsules containing a highly concentrated acetaminophen solution. The invention, involves use of alkali metal acetate to improve solubility of acetaminophen in a solution containing polyethylene glycol, polypropylene glycon and water. US patent 5510389 deals with concentrated acetaminophen solution compositions. Use of propylene glycol along with polyethylene glycol and polyvinyl pyrolidine improves solubility. Patent no. 5071643 is for solvent system enhancing the solubility of pharmaceuticals for encapsulation. It involves use of gelling agents like sodium stearate, sodium palmitate and calcium acetate to improve solubility of pharmaceutical ingredients into polyethylene glycol.

US patent 6287594 discloses oral liquid compositions with improved Bioavailability. They are designed to provide drugs with minimal gastric irritability wherein ratio of active drug to polymer based dispersing agent is from about 3:1 to 1:50 w/w. The resulting solution is found to be hazy. Polyvinyl pyrolidone is dispersing agent described. The purpose of invention is not to provide a clear solution.

US patent 6383515 provides a medicament in concentration of 49% to 70 % wherein solvent system comprises of low molecular weight polymer and organic acid. It involves heating as a part of process. The process may, may not result in a clear solution as disclosed in examples.

US patent 6387400 discloses a process for improving concentration of a pharmaceutically active ingredient relative to fill composition. It comprises of two step addition process. In step one a suspension of part of a drug is made in polyethelene glycol with a molecular weight of 200 daltons to 100,000 daltons and solubilizing it subsequently with hydroxide ion: In step two remaining drug is added and resulting suspension is solubilized by adding remaining part of hydroxide ion. The ratio of a drug to fill material by weight is 1:2 and/or 5:9.

US patent 5919, 481 discloses fill material for soft gelatin capsule which is translucent, semisolid in nature. It uses poly alkylene glycol with average molecular weight of about 600 or less along with cellulose ether.

The US patent 5141961 discloses a process for solubilizing difficulty soluble pharmaceutical actives. It uses polyethelene glycol, polyvinyl pyrolidine and monohydric alcohols. The ratio of polyethylene glycol to polyvinyl pyrolidine is about 2.5 to 1. It does not involve use of heat. It does not require use of solvent and surfactants.

PCT Application No. W088/02625, to Yu et al., published Apr. 21, 1988 which discloses the solubilization of an ionized or partly-ionized pharmaceutical active in a mixture of water.

The present invention provides a process by which clear solution of poorly soluble pharmaceutical substances is obtained wherein the amount of pharmaceutical substance is increased compared to conventional pharmaceutical compositions available.

In many instances it may not be possible or desirable to incorporate, water-miscible co-solvents, or surfactants into a pharmaceutical composition. For example, water-miscible co-solvents, such as ethanol, have the disadvantage of being relatively volatile, thereby resulting in concentration changes in the actives over time. Also, these co-solvents may not be compatible with the desired pharmaceutical actives. A more important disadvantage of volatile water-miscible co-solvents is that they are incompatible with soft gelatin capsules. Even though it may be possible to prepare soft gelatin capsules containing these solvents, over time the capsules gradually soften and deform, and develop leaks as these solvents dissolve the soft gelatin shell. Thus, it would be highly desirable to develop a solubilization process water-miscible co-solvents are used, it would be highly desirable to develop a process in which the water-miscible solvents are ultimately removed from the final compositions.

The present invention uses a combination of polyethylene glycol with different molecular weight with polymer and water. Polyethylene glycol(PEG) used as per the present invention is a mixture of PEG with different molecular weights. Polymer is any polymer, including polyvinyl pyrolidone.

The process as per the present invention does not use any alkalizing substance, surfactant to increase content of poorly soluble pharmaceutical ingredients as a clear liquid solution for encapsulation in a soft gelatin capsule.

As per the present invention it is possible to obtain a stable clear liquid solution of acetaminophen using PEG and PVP alone, wherein the concentration of acetaminophen is more than 30%.

It is not possible to make a clear solution of acetaminophen to a concentration more than 27% without using hydroxide, alkalizing substance, surfactant or propylene glycol.
It is therefore an object of the present invention to provide a process for solubilizing poorly soluble pharmaceutical actives. Another object of the present invention is to provide a solubilization process which does not require hydroxide, alkalizing agent, or surfactants. A further object of the present invention is to provide pharmaceutical compositions containing increased poorly soluble pharmaceutical actives.

These and other objects of this invention will become apparent in light of the following disclosure.

SUMMARY OF THE INVENTION

The invention herein provides for a process whereby the concentration of pharmaceutically active ingredients is improved in clear solution which can be used for encapsulation in a soft gelatin capsule. This permits the use of reduced overall fill volumes or alternatively, higher concentrations of the active ingredient per dosage unit or form.
The process according to the present invention increases the achievable concentration of pharmaceutically active ingredient in a clear liquid solution which can be used for encapsulation of soft gelatin capsule comprises use of two or more polyethelene glycol with different molecular weight and polyvinyl pyrolidone.

Thus there is disclosed process of increasing concentration of pharmaceutically cative ingredient in a clear liquid solution comprising the steps of

a. Mixing polyethylene glycol of different molecular weights in the range of about 40% to about 60% of the total weight.
b. Addition of water while stirring to step a.
c. Addition of dispersing agents like polyvinyl pyrrolidine while stirring in a range of about 4% to about 8% to the liquid obtained from step b.
d. Addition of poorly soluble active pharmaceutical ingredients while stirring to the liquid obtained from step c.
e. Heating of a resultant mixture obtained from step d while stirring at temperature not exceeding 90 ^{0}C.

Pharmaceutical active ingredients suitable for use invention including but not limited to acetaminophen, acetylsalicylic acid, ibuprofen, fenbrprofen, flurbiprofen, indomethacin, naproxen, and mixture thereof.

Polyethelene glycols which can be used in accordance with present invention include those having molecular weight range from about 200 daltons to about 100000 daltons. Preferable two polyethelene glycol as per present invention are those having average molecular weight of 400 daltons and 1000 daltons.

Polyvinyl pyrolidone is used in present invention can also have a wide ranging molecular weight most preferred poly vinyl pyrolidone has molecular weight of about 30,000(k 30)

The heating is required to achieve a clear liquid solution. Heating should not exceed 90^0c. It is preferable done between 60^0c to 80^0c.

The invention provides clear liquid solution with increased content of active pharmaceutical ingredient comprising:

a. from about 15% to about 40% of at least one poorly soluble pharmaceutical active;
b. from about 40% to about 60% of a polyethylene glycol;
c. from about 4% to about 8% of a polyvinyl pyrolidine; and
d. from about 5% to about 10% water, wherein the ratio of poltethylene glycol to polyvinyl pyrolidine is from 4:1 to 15:1.

The pharmaceutical composition and soft gelatin capsule made as per present invention are stable for more than two years under standard stability conditions and self life

DETAILED DESCRIPTION OF THE INVENTION

The polyethylene glycols useful herein are those which are liquids at room temperature or have a melting point slightly there above. Preferred are the polyethylene glycols having a molecular weight range from about 300 to about 1000. More preferred are the polyethylene glycols having a molecular weight range from about 400 to about 1000. Most preferred is a polyethylene glycol having a molecular weight of about 600 and 1000.
If only a low molecular weight. PEG is used, the poorly soluble drug are either become turbid or precipitate. I a high molecular weight PEG, with poorly soluble drugs are not formed a clear liquid. To get clear concentrated liquid preparation, a mixture of low and high molecular height PEG are better, therefore, mixtures of two or more polyethylene glycols of different average molecular weight range can also be employed in the present invention.

The process for preparing the highly concentrated liquid compositions of the present invention comprises adding from about 40% to about 60% polyethylene glycol.

An essential component of the present compositions is polyvinylpyrrolidone ("PVP"), which is a polymer of N-vinyl-2-pyrrolidone

The soluble forms of polyvinylpyrrolidone are preferred for use in the present invention. Preferred are soluble polyvinylpyrrolidones having an average molecular weight in the range from about 2900 to about 1,100,000; more preferred are those having an average molecular weight in the range from about 9000 to about 45,000; and most preferred are those having an average molecular weight of about 30,000 (k-30). Moreover, mixtures of two or more soluble polyvinylpyrrolidones of different average molecular weight can be employed.

The process disclosed in the present invention for preparing the highly concentrated liquid compositions of the instant invention comprises adding from about 4% to about 8% of a soluble polyvinylpyrrolidone.

With the use of PVP in combination with PEGs there is a definite increase the solubility of poorly soluble drugs. If heating is given to the mixture of poorly soluble drugs along with PVP and PEG, the solubility of poorly soluble drugs can be further increased.

EXAMPLE I

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	325.00	6.500
2. Pseudoephedrine hydrochloride	32.25	0.645
3. Chlorpheniramine Maleate	2.15	0.043
4. Polyethylene glycol 400	510.60	10.212
5. Polyethylene glycol 1000	30.00	0.600
6. Purified water	75.00	1.500
7. Poly vinyl pyrolidine 1.100	55.00	
Total Weight	1030 mg	20.600 Kg

Process :

Take 10.212 Kg of polyethylene glycol 400 (PEG 400) and filter through 80 mesh stainless steel sieve in to a stainless steel jacketed tank with impeller type stirrer. Take 1.500 Kg purified water and add to the PEG 400 after filtering through 80 mesh stainless steel sieve. To the mixture of PEG 400 and purified water, slowly add 0.600 Kg of polyethylene glycol 1000 with stirring. The resultant mixture is subjected to heating up to 70 ^{0}C and mix for 10 minutes. Take 1.100 Kg Poly vinyl pyrolidine and pass through 40 mesh stainless steel sieve and add slowly to the above mixture with constant stirring till clear liquid obtains. Take 6.500 Kg of Acetaminophen, 0.645 Kg of Pseudoephedrine hydrochloride and 0.043 Kg of Chlorpheniramine Maleate and separately pass through a 60 mesh stainless steel sieve with the help of mechanical vibratory shifter. Add Acetaminophen, Pseudoephedrine hydrochloride and Chlorpheniramine Maleate one after another to the clear liquid obtained above with constant stirring. After addition of all the ingredients, heat the mixture slowly up to a maximum of 90 ^{0}C with constant stirring till clear liquid obtained. Filter the clear liquid through 200 mesh stainless steel sieve and allow the liquid to cool up to 25 ^{0}C. After cooling, the liquid is subjected to de aerate under a vacuum pressure between 630 mm hg to 670 mm Hg. This liquid is ready for encapsulation in a soft gelatine shell. All blending and mixing operations are carried out at relative humidity from 25% to 35%.

EXAMPLE II

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	325.00	6.500
2. Pseudoephedrine hydrochloride	32.25	0.645
3. Dextromethorphan Hydrobromide	10.75	0.215
4. Doxylamine Succinate	6.72	0.1344
5. Polyethylene glycol 400	515.28	10.306
6. Polyethylene glycol 1000	30.00	0.600
7. Purified water	75.00	1.500
8. Poly vinyl pyrolidine 1.100	55.00	
Total Weight	1050 mg	21.000 Kg

Process :

Take 10.306 Kg of polyethylene glycol 400 (PEG 400) and filter through 80 mesh stainless steel sieve in to a stainless steel jacketed tank with impeller type stirrer. Take 1.500 Kg purified water and add to the PEG 400 after filtering through 80 mesh stainless steel sieve. To the mixture of PEG 400 and purified water, slowly add 0.600 Kg of polyethylene glycol 1000 with stirring. The resultant mixture is subjected to heating up to 70 ^{0}C and mix for 10 minutes. Take 1.100 Kg Poly vinyl pyrolidine and pass through 40 mesh stainless steel sieve and add slowly to the above mixture with constant stirring till clear liquid obtains. Take 6.500 Kg of Acetaminophen, 0.645 Kg of Pseudoephedrine hydrochloride, 0.215 Kg of Dextromethorphan Hydrobromide and 0.1344 Kg of Doxylamine Succinate and separately pass through a 60 mesh stainless steel sieve with the help of mechanical vibratory shifter. Add Acetaminophen, Pseudoephedrine hydrochloride, Dextromethorphan Hydrobromide and Doxylamine Succinate one after another to the clear liquid obtained above with constant stirring. After addition of all the ingredients, heat the mixture slowly up to a maximum of 90 ^{0}C with constant stirring till clear liquid obtained. Filter the clear liquid through 200 mesh stainless steel sieve and allow the liquid to cool up to 25 ^{0}C. After cooling, the liquid is subjected to de aerate under a vacuum pressure between 630 mm hg to 670 mm Hg. This liquid is ready for encapsulation in a soft gelatine shell. All blending and mixing operations are carried out at relative humidity from 25% to 35%.

EXAMPLE III

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	325.00	6.500
2. Pseudoephedrine hydrochloride	32.25	0.645
3. Dextromethorphan Hydrobromide	10.75	0.215
4. Polyethylene glycol 400	512.75	10.240
5. Polyethylene glycol 1000	30.00	0.600
6. Purified water	75.00	1.500

7. Poly vinyl pyrolidine 1.100		55.00	
Total Weight	1040 mg		20.800 Kg

Process :

Take 10.240 Kg of polyethylene glycol 400 (PEG 400) and filter through 80 mesh stainless steel sieve in to a stainless steel jacketed tank with impeller type stirrer. Take 1.500 Kg purified water and add to the PEG 400 after filtering through 80 mesh stainless steel sieve. To the mixture of PEG 400 and purified water, slowly add 0.600 Kg of polyethylene glycol 1000 with stirring. The resultant mixture is subjected to heating up to 70 ^{0}C and mix for 10 minutes. Take 1.100 Kg Poly vinyl pyrolidine and pass through 40 mesh stainless steel sieve and add slowly to the above mixture with constant stirring till clear liquid obtains. Take 6.500 Kg of Acetaminophen, 0.645 Kg of Pseudoephedrine hydrochloride and 0.215 Kg of Dextromethorphan Hydrobromide and separately pass through a 60 mesh stainless steel sieve with the help of mechanical vibratory shifter. Add Acetaminophen, Pseudoephedrine hydrochlorlde and Dextromethorphan Hydrobromide one after another to the clear liquid obtained above with constant stirring. After addition of all the ingredients, heat the mixture slowly up to a maximum of 90 ^{0}C with constant stirring till clear liquid obtained. Filter the clear liquid through 200 mesh stainless steel sieve and allow the liquid to cool up to 25 ^{0}C. After cooling, the liquid is subjected to de aerate under a vacuum pressure between 630 mm hg to 670 mm Hg. This liquid is ready for encapsulation in a soft gelatine shell. All blending and mixing operations are carried out at relative humidity from 25% to 35%.

EXAMPLE IV

Ingredients	Quantity per capsule (mg)		Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	325.00		6.500
2. Pseudoephedrine hydrochloride	32.25		0.645
3. Polyethylene glycol 400	512.75		10.255
4. Polyethylene glycol 1000	30.00		0.600
5. Purified water	75.00		1.500
6. Poly vinyl pyrolidine 1.100		55.00	
Total Weight	1040 mg		20.600 Kg

Process :

Take 10.255 Kg of polyethylene glycol 400 (PEG 400) and filter through 80 mesh stainless steel sieve in to a stainless steel jacketed tank with impeller type stirrer. Take 1.500 Kg purified water and add to the PEG 400 after filtering through 80 mesh stainless steel sieve. To the mixture of PEG 400 and purified water, slowly add 0.600 Kg of polyethylene glycol 1000 with stirring. The resultant mixture is subjected to heating up to 70 ^{0}C and mix for 10 minutes. Take 1.100 Kg Poly vinyl pyrolidine and

pass through 40 mesh stainless steel sieve and add slowly to the above mixture with constant stirring till clear liquid obtains. Take 6.500 Kg of Acetaminophen, 0.645 Kg of Pseudoephedrine hydrochloride and separately pass through a 60 mesh stainless steel sieve with the help of mechanical vibratory shifter. Add Acetaminophen, Pseudoephedrine hydrochloride one after another to the clear liquid obtained above with constant stirring. After addition of all the ingredients, heat the mixture slowly up to a maximum of 90 ^{0}C with constant stirring till clear liquid obtained. Filter the clear liquid through 200 mesh stainless steel sieve and allow the liquid to cool up to 25 ^{0}C. After cooling, the liquid is subjected to de aerate under a vacuum pressure between 630 mm hg to 670 mm Hg. This liquid is ready for encapsulation in a soft gelatine shell. All blending and mixing operations are carried out at relative humidity from 25% to 35%.

EXAMPLE V

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	325.00	6.500
2. Pseudoephedrine hydrochloride	32.25	0.645
3. Dextromethorphan Hydrobromide	10.75	0.215
4. Chlorpheniramine maleate	2.15	0.043
4. Polyethylene glycol 400	519.85	10.397
5. Polyethylene glycol 1000	30.00	0.600
6. Purified water	75.00	1.500
7. Poly vinyl pyrolidine 1.100	55.00	
Total Weight	1050 mg	21.000 Kg

Process :

Take 10.397 Kg of polyethylene glycol 400 (PEG 400) and filter through 80 mesh stainless steel sieve in to a stainless steel jacketed tank with impeller type stirrer. Take 1.500 Kg purified water and add to the PEG 400 after filtering through 80 mesh stainless steel sieve. To the mixture of PEG 400 and purified water, slowly add 0.600 Kg of polyethylene glycol 1000 with stirring. The resultant mixture is subjected to heating up to 70 ^{0}C and mix for 10 minutes. Take 1.100 Kg Poly vinyl pyrolidine and pass through 40 mesh stainless steel sieve and add slowly to the above mixture with constant stirring till clear liquid obtains. Take 6.500 Kg of Acetaminophen, 0.645 Kg of Pseudoephedrine hydrochloride and 0.215 Kg of Dextromethorphan Hydrobromide and0.043 kg of Chlorpheniramine maleate separately pass through a 60 mesh stainless steel sieve with the help of mechanical vibratory shifter. Add Acetaminophen, Pseudoephedrine hydrochloride and Dextromethorphan Hydrobromide and Chlorpheniramine maleate one after another to the clear liquid obtained above with constant stirring. After addition of all the ingredients, heat the mixture slowly up to a maximum of 90 ^{0}C with constant stirring till clear liquid obtained. Filter the clear liquid through 200 mesh stainless steel sieve and allow the liquid to cool up to 25 ^{0}C. After cooling, the liquid is subjected to de aerate under a vacuum pressure between 630 mm hg to 670 mm Hg. This liquid is ready for encapsulation in a soft gelatine shell. All blending and mixing operations are carried out at relative humidity from 25% to 35%.

Propylene glycol may be used in above process. However its amount should not increase more than 2%. Otherwise solution looses its clarity.

As per present invention substitution of polyvinyl pyrolidone by surfactants like Tween-80, Tween 40, Hydrogenated castor oil derivatives like cremaphor RH-40, Cremaphor EL results in loss of clarity of a solution.

Following examples demonstrates the limitation of present process in obtaining concentrated clear liquid pharmaceutical composition of poorly soluble

pharmaceutical active ingredients. All of below mentioned compositions are either no clear or loose their clarity during there self life.

EXAMPLE I

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400	530.00	10.600
3. Polyethylene glycol 1000	30.00	0.600
4.PVP(k 30)	55	1.100
6. Purified water	75.00	1.500
Total Weight	1090 mg	21.800 Kg

EXAMPLE II

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400	530.00	10.600
3. Polyethylene glycol 1000	35.00	0.700
4.PVP(k 30 + k90)	57.5 + 27.5	1.100
6. Purified water	75.00	1.500
Total Weight	1125 mg	21.8 Kg

EXAMPLE III

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400	530.00	10.600
3. Polyethylene glycol 1000	30.00	0.600
4.PVP(k 90)	55	1.100
6. Purified water	80.00	1.600
Total Weight	1095 mg	21.900 Kg

EXAMPLE IV

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	450.00	9.000
2. Polyethylene glycol 400	550.00	11.000
3. Polyethylene glycol 1000	30.00	0.600
4.PVP(k 90)	60	1.200
5. Purified water	85.00	1.700
Total Weight	1175 mg	23.500 Kg

EXAMPLE V

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400(495)	45%	10.600
3. Polyethylene glycol 1000(66)	6%	0.600
4.PVP(k 30)	55	1.100
5. Purified water	75.00	1.500
Total Weight	1100 mg	21.8 Kg

EXAMPLE VI

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400(522)	47.5%	10.600
3. Polyethylene glycol 1000(29.2)	2.7%	0.600
4.PVP(k 30)	55	1.100
5. Purified water	75.00	1.500

EXAMPLE VII

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)

1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400(495)	45%	10.600
3. Polyethylene glycol 1450(44)	4%	0.600
4.PVP(k 30)	55	1.100
5. Purified water	75.00	1.500

EXAMPLE VIII

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400	520	10.400
3. Polyethylene glycol 1000	30	0.600
4.PVP(k 30)	90	1.800
5. Purified water	75.00	1.500
6. Potassium Acetate	6	0.120
Total Weight	1121 mg	22.420Kg

EXAMPLE IX

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	450.00	8.000
2. Polyethylene glycol 400	400	10.600
3. Polyethylene glycol 200	120	
4. Polyethylene glycol 1450	44	0.600
5.PVP(k 30)	90	1.100
6. Purified water	75.00	1.500
Total Weight	1179 mg	21.8Kg

EXAMPLE XI

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400	483.00	0.966
3. Polyethylene glycol 1500	29.00	0.580
4. PVP(k 90)	63	1.260
5. Purified water	175.00	3.500
Total Weight	1217mg	14.306Kg

EXAMPLE XII

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	500.00	10.000
2. Polyethylene glycol 400	483.00	0.966
3. Polyethylene glycol 1500	29.00	0.580
4. PVP(k 90)	63	1.260
5. Purified water	175.00	3.500
Total Weight	1250mg	16.306Kg

EXAMPLE XIII

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	10.000
2. Polyethylene glycol 400	483.00	0.966
3. Polyethylene glycol 1500	29.00	0.580
4. PVP(k 90)	63	1.260
5. Purified water	175.00	3.500
Total Weight	1250mg	16.306Kg

We Claim

1. The process of manufacturing pharmaceutical composition with increased content of poorly soluble pharmaceutical ingredients in a clear liquid solution comprising the steps of:
   a. Preparing a solvent system comprising of at least two from polyethylene glycol of different molecular weights in the range of about 40% to about 60% of the total weight, water, and dispersing agents like polyvinyl pyrrolidine in a range of about 4% to about 8%.
   b. Addition of poorly soluble active pharmaceutical ingredients while stirring to the liquid obtained from step a.
   c. Heating of a resultant mixture obtained from step b while stirring at temperature not excceding 90 ^{0}C.
2. The process according to claim 1 wherein the pharmaceutically active ingredient ranges from about 15% to about 40%.
3. The process according to claim 2 wherein the pharmaceutical active ingredient ranges from about 25% to about 33%.
4. The process according to claim 1 wherein at least one of the polyethylene glycol have average molecular weight below 600.
5. The process according to claim 1 wherein one of the polyethylene glycol have average molecular weight is 400.
6. The process according to claim 1 wherein at least another polyethylene glycol should have molecular weight of 800 or above.
7. The process according to claim 4 wherein at least another polyethylene glycol should have molecular weight of 1000 or above.
8. Polyethylene glycol with molecular weight lower than 600 as claimed in claim 4 should be 85% or above of total polyethylene glycol.
9. The process according to claim 8 wherein polyethylene glycol with molecular weight lower than 600 should be 88% or above of total polyethylene glycol.
10. The process according to claim 8 wherein polyethylene glycol with molecular weight lower than 600 should be 92% or above of total polyethylene glycol.
11. The process according to claim 1 wherein polyethylene glycol with high molecular weight should be 15% or less of total polyethylene glycol.
12. The process according to claim 11 wherein polyethylene glycol with high molecular weight should be at least 3% of total polyethylene glycol.
13. The process according to claim 11 wherein polyethylene glycol with high molecular weight should be at least 5% of total polyethylene glycol.
14. The process according to claim 1 wherein the ratio of polyethylene glycol to polyvinyl pyrolidine is about 4:1 to 15:1.
15. The process according to claim 14 wherein the ratio of polyethylene glycol to polyvinyl pyrolidine is about 4:1 or above.
16. The process according to claim 14 wherein the ratio of polyethylene glycol to polyvinyl pyrolidine is about 5:1 or above.
17. The process according to claim 14 wherein the ratio of polyethylene glycol to polyvinyl pyrolidine is about 6:1 or above.
18. A process according to claim 1 wherein poorly soluble active pharmaceutical ingredients is selected from the group consisting of acetaminophen, acetylsalicylic acid, ibuprofen, fenbrprofen, flurbiprofen, indomethacin, naproxen, and mixture thereof.
19. A process according to claim 18 wherein the poorly soluble active pharmaceutical ingredient is acetaminophen.

20. A process according to claim 1 which further comprises combining in step (b) form about 0.5% to 20% of a second pharmaceutical active ingredient selected from the group consisting of dextromethorphan hydrobromide, doxyllamine succinate, pseudoephedrine hydrochloride, chlorpheniramine maleate, guaifenesin, tripolidine hydrochloride, diphenhydramine hydrochloride, and mixture thereof.
21. A process of manufacturing pharmaceutical composition with increased content of poorly soluble pharmaceutical ingredients in a clear liquid solution comprising the steps of:
    a. Preparing a solvent system comprising of at least two from polyethylene glycol of different molecular weights in the range of about 40% to about 60% of the total weight, water, and dispersing agents like polyvinyl pyrrolidine in a range of about 4% to about 8%.
    b. Addition of poorly soluble active pharmaceutical ingredients while stirring to the liquid obtained from step a.
    c. Heating of a resultant mixture obtained from step b while stirring at temperature not exceeding 90 ^{0}C.
    d. Encapsulating the clear liquid composition in a soft gelatin shell.
22. A process according to claim 21 wherein poorly soluble active pharmaceutical ingredients is selected from the group consisting of acetaminophen, acetylsalicylic acid, ibuprofen, fenbrprofen, flurbiprofen, indomethacin, naproxen, and mixture thereof.
23. A process according to claim 21 which further comprises combining in step (b) form about 0.5% to 20% of a second pharmaceutical active ingredient selected from the group consisting of dextromethorphan hydrobromide, doxyllamine succinate, pseudoephedrine hydrochloride, chlorpheniramine maleate, guaifenesin, tripolidine hydrochloride, diphenhydramine hydrochloride, and mixture thereof.
24. A concentrated clear liquid , pharmaceutical composition prepared in accordance with the process of claim 1.
25. A concentrated clear liquid , pharmaceutical composition prepared in accordance with the process of claim 18.
26. A concentrated clear liquid , pharmaceutical composition prepared in accordance with the process of claim 20.
27. A soft gelatin capsule prepared in accordance with the process of claim 21.
28. A soft gelatin capsule prepared in accordance with the process of claim 22.
29. A soft gelatin capsule prepared in accordance with the process of claim 23.
30. A concentrated clear liquid, pharmaceutical composition which is comprising,
    a. from about 15% to about 40% of at least one poorly soluble pharmaceutical active;
    b. from about 40% to about 60% of a polyethylene glycol;
    c. from about 4% to about 8% of a polyvinyl pyrolidine; and
    d. from about 5% to about 10% water, wherein the ratio of poltethylene glycol to polyvinyl pyrolidine is from 4:1 to 15:1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 02/03015

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A61K 9/66, 47/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0679395 A1 (BAYER S.P.A.) 2 November 1995 (02.11.95) *the whole document.*	1-30

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
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„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2002 (13.11.2002)	4 December 2002 (04.12.2002)
Name and mailing adress of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer KRENN M. Telephone No. 1/53424/435

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IB 02/03015-0

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